DETAILED ACTION

1. The Amendment filed 06/09/2011 in response to the Office Action of 12/09/2010 is acknowledged and has been entered. Claims 1-10 and 13-15 are pending, claim 7 has been amended, claims 1-6 and 13-15 were previously withdrawn and claims 11-12 were cancelled. Claims 7-10 are currently being examined.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claim 10 remains rejected under 35 U.S.C. 103 (a) as being unpatentable over Bertolesi et al. (Mol. Pharmacol. 62:210–219, 2002, hereafter Bertolesi)) in view of Gray et al. (U. S. Patent Number 6413967, hereafter '967) for the reason of record set forth below.

Claims 7-8 and 10: Bertolesi teaches mibefradil has additive effects on T type Ca^{2+} channel current inhibition (abstract), this meets with claim 7; Mibefradil is a benzimidazolyl-substituted tetraline derivative (page 210, paragraph 1, line 3), this meets claims 8; Mibefradil has also been reported to inhibit the proliferation of various cell types, including blood mononuclear cells, rat smooth muscle cells, mouse liver cells, endothelial cells and retinoblastoma and MCF7 breast cancer cells (Fig.1), this meets with claim 10; Mibefradil was reported to prevent neointima formation after vascular injury in rats (page 218, paragraph 2, line 1-11); Mibefradil induces cell death in retinoblastoma and MCF7 breast cancer cells by different pathways, the mechanism of cell death was primarily necrotic and largely dependent on block of T type Ca^{2+} channels (page 217, right column of the first paragraph, line 15-18). The limitation of Bertolesi is that the treatment and prevention of cancer cells is for cancer patient. Bertolesi doesn't teach cancer patient.

'967 teaches lymphocytes, epithelial cells, connective tissue cells, secretory cells and PC-3 (a prostate cancer cell line) which lack the type of electrical activity occurring in electrically excitable cells and so are named "electrically non-excitable"; the calcium channels in these

types of cell are also referred to as voltage gated (VG) channels by the inventors [BACKGROUND OF THE INVENTION, Column 1, line 45-49; DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS, column 5, line 34-38); for inhibiting calcium entry into electrically non-excitable cells with said VG-selective inhibitors, methods for preventing proliferation of electrically non-excitable cells with said VG-selective inhibitors as well as methods of treating cancer (abstract). '967 further teaches that "treating" means ameliorating a disease such that the condition of the patient improves or such that the progress of the disease is slowed, the beneficial effects of the VG-selective inhibitors of the present invention can be determined by monitoring an improvement in one or more symptoms; for example, by monitoring the decrease in proliferation (cancer) [DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS, column 10, line 55-61]; these statement meet claims 7-8 and 10 which administering to a patient. The limitation of '967 is that it doesn't teach the inhibitor is mibefradil. Therefore, it would have been obvious to have the mibefradil to inhibit T type calcium channel cancer cells proliferation of Bertolesi taught with electrically non-excitable cells (lymphocytes and epithelial cells *et*) and treatment of cancer patient as taught by '967, because '967 satisfies the limitation of Bertolesi taught.

Applicant's arguments:

Claims 7-8 and 10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Bertolesi et al. (Mol. Pharmacol. 62:210-219, 2002, hereafter Bertolesi) in view of Gray et al. (U.S. Patent Number 6413967, hereafter '967). Applicant respectfully traverses this rejection.

Bertolesi et al. specifically reject the hypothesis that T type calcium blockers inhibit proliferation by cell cycle arrest and cytostasis (page 214 section beginning in left column titled "Cytostatic or Cytotoxic Effects of Pimozide and Mibefradil"). Instead, they interpret their experimental results to indicate that these drugs block proliferation by inducing cell death. A basic tenet of the present application is that inhibition by T type calcium blockers is by inducing cell cycle blockade and inducing cytostasis. Cytostatic and cytotoxic are fundamentally different. Conventional cancer chemotherapeutic agents are cytotoxic, which has implications for the clinical approach to therapy. Cytotoxic drugs are administered intermittently while cytostatic drugs are given chronically. Cytotoxic drugs cause collateral damage to normal, healthy tissues, which bring dose and schedule limiting toxicities. This is not true with cytostatic regimens. Cytotoxicity and cytostasis are mechanistically dichotomous such that implication of one mechanism necessarily excludes the other.

As such, Applicant respectfully submits that Bertolesi et al. do not disclose or suggest inducing cyctostasis or inducing cytostatis in a patient (claim 7). Applicant respectfully submits that the secondary reference, Gray et al., does not remedy the deficiencies of Bertolesi et al. Thus, Applicant respectfully requests withdrawal of this rejection under 103.

Claims 9 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Bertolesi et al. (Mol. Pharmacol. 62:210-219, 2002, hereafter Bertolesi)) in view of Gray et al. (U. S. Patent Number 6413967, hereafter '967), as applied to claim 7 above, and further in view of Lewin et al. (U. S. Patent Application Publication 2006/0110332, hereafter '332). Applicant respectfully traverses this rejection.

Bertolesi is discussed above. Applicant respectfully submits that the secondary references, Gray et al. and Lewin et al., do not remedy the deficiencies of Bertolesi et al. Thus, Applicant respectfully requests withdrawal of this rejection under 103.

Applicant's arguments have been considered, but have not been found persuasive, because claim 10 is not drawn to inducing cytostasis. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claim 10, given its broadest reasonable interpretation encompasses treating with cytotoxic agents and a cytotoxic agent will inhibit cell proliferation, i.e. the cells are not alive to proliferate. Thus, the rejection is maintained for the reasons of record.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7-9 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. This is a new matter rejection.

Claims 7-9 are drawn to a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of mibefradil so as to induce cytostasis in said patient.

Presently amended claim 7 states a method for "inducing cytostasis" and "so as to induce cytostasis in said patient". There is no support for these claim limitations found in the specification such as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of inducing cytostasis by mibefradil in said patient. The examiner invites applicant to point to the specific paragraph where support for "inducing cytostasis" and "so as to induce cytostasis in said patient" may be found. Amended claim 7 has no clear support in the specification and the claims as originally filed.

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See MPEP 2163.05 (II). See also *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ("Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." Thus the limitation of "inducing cytostasis" and "so as to induce cytostasis in said patient" is new matter because it is not supported by the as-filed disclosure.

4. Claims 7-9 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 7-9 are drawn to a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of mibefradil so as to induce cytostasis in said patient.

> The specification teaches:
> 0011] Accordingly, one aspect of the present invention is directed to a method of inhibiting cancer cell growth or proliferation comprising administering to a patient in need thereof a therapeutically effective amount of T type calcium channel selective inhibitor.
>
> [0051] mibefradil inhibits proliferation of electrically non-excitable cancer cells by inhibiting calcium entry into them, as shown in FIGS. 1A to 1F.

One of skill in the art cannot extrapolate the teachings of the specification to enable the claims because the claims are drawn to a method for inducing cytostasis comprising administering to a patient in need thereof a therapeutically effective amount of mibefradil so as

to induce cytostasis in said patient; however, the specification has only presented data showing that mibefradil inhibits proliferation of prostate cancer cell lines *in vitro*; the specification presents no examples to demonstrate that mibefradil can induce cytostasis in cells or in a patient.

As applicant point out that in the remarks of 06/09/2011:

"Cytostatic and Cytotoxic are fundamentally different. Conventional cancer chemotherapeutic agents are cytotoxic, which has implications for the clinical approach to therapy. Cytotoxic drugs are administered intermittently while cytostatic drugs are given chronically. Cytotoxic drugs cause collateral damage to normal, healthy tissues, which bring dose and schedule limiting toxicities. This is not true with cytostatic regimens. Cytotoxicity and cytostasis are mechanistically dichotomous such that implication of one mechanism necessarily excludes the other".

Additionally, Bertolesi et al. (cited above) provides evidences that mibefradil inhibits cell growth via cytotoxic mechanisms. See title, abstract, page 214. It is noted that the specification does not show that the inhibition of cell proliferation observed is cytostatic not cytotoxic. The doses at which Applicants observe any effect, great than 10 microM, is at least 10 times the dose Bertolesi et al. shows to be cytotoxic. See Fig. 1 of instant app. and Fig. 4 of Bertolesi et al. Thus, one of skill in the art would not be able to make and use the method as claimed to induce cytostasis in cells or in a patient with mibefradil.

Thus, based on the evidence that mibefradil inhibits cell growth via cytotoxic mechanisms not cytostatic mechanisms as taught by Bertolesi et al., and based on the cell culture data presented in the specification, in the absence of data provided from appropriate *in vivo*

models and in the absence of data that mibefradil could induce cytostasis in cells *in vitro* or in patient, one of skill in the art would not be able to make and use the method as claimed for inducing cytostasis in cells or in a patient.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples and/or evidence which would provide guidance to one skilled in the art and would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

Claim Objections

5. Claims 7 and 10 are objected to because of the following informalities:

Claim 7: should be an "of" between "amount" and "T" in claim 7.

Claim 10 the word "call" should be "cell".

Appropriate correction is required.

6. All other objections and rejections recited in Office Action of 12/09/2010 are withdrawn in light of applicant's amendments and/or arguments.

7. No claims allowed.

8. Applicant's amendment necessitated the new grounds of rejection. Thus **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YAN XIAO whose telephone number is (571)270-3578. The examiner can normally be reached at 7:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, Primary Examiner, Peter Reddig (571-272-9031), or the examiner's supervisor, Misook Yu (571-272-0839) can be reached. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/YAN XIAO/
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